REMARKS

Claims 27, 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, and 72-75 were pending in this application. Claims 27 and 72-75 have been canceled as being drawn to non-elected subject matter. Applicants reserve the right to prosecute the subject matter of the non-elected claims in one or more continuing applications.

Claims 56 and 60 have been amended to clarify that which Applicants regard as the invention. Specifically, claims 56 and 60 have been amended to be dependent upon 38 or 54. New claim 76, directed to a method of the invention wherein the nucleotide sequence encodes human IL-12, has been added. New claim 77, directed to a method of the invention wherein the 4-1BB ligand is human 4-1BB ligand, has been added. New claim 78, directed to a method of the invention wherein the subject is a non-human mammal, has been added. New claims 79-81, directed to methods of the invention wherein the subject is a human, have been added. New claim 82, directed to a method of the invention wherein the adenovirus is administered intratumorally, has been added. New claim 83, directed to a method of the invention wherein the adenovirus is administered intranasally, has been added. Support for the amendments and new claims can be found in the specification, for example, at page 12, lines 13-25, page 13, lines 9-10, page 29, lines 18-19, page 34, lines 27-30, and page 35, lines 2-3. No new matter has been added by these amendments. After entry of the present amendment, claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, and 76-83 will be pending.

Entry of the foregoing amendments and consideration of these remarks is respectfully requested.

I. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

A. The Rejection of Claims 38-71 Under 35 U.S.C. § 112, First Paragraph for Lack of Enablement has been Obviated

Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, and 70 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner contends that the specification fails to provide enablement for using any type of nucleic acid administered by any route.

In the Office Action of November 7, 2003, claims 38-71 were rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contended that the specification failed to provide enablement for routes of administering IL-12 encoding nucleic acid molecules other than intratumoral administration. In response, Hirschowitz *et al.* (1999, Am. J. Respir. Cell Mol. Biol. 20:935-941; "Hirschowitz") and Siders *et al.* (1998, J. Immunol. 160:5465-5474; "Siders") were provided as evidence that an adenoviral vector could be used in routes of administration other than intratumorally.

The Examiner now contends that, while Hirschowitz and Siders support systemic delivery of adenoviral vector to lung tissue or liver, they do not support the full scope of the claims drawn to using any type of nucleic acid administered via any route. As support, the Examiner contends that adenovirus is known for tissue tropism to epithelial cells of the respiratory system such as lung and hepatocytes in the liver. The Examiner cites Siders and Gregory *et al.* (U.S. Pat. No. 6,093,567) as teaching the use of adenovirus vectors for delivery to liver tissue or lung, respectively. The Examiner cites Worth *et al.* (2000, Clin. Cancer Res. 6:3713-8; "Worth") as support for unpredictable efficacy because no expression in seen in the liver when the adenoviral vector is administered intranasally. The Examiner concludes that transgene expression is associated with the type of nucleic acid used and the routes of administration.

The Examiner goes on to state that vectors have unpredictable efficacy in infecting/transfecting target cells/tissue and that it is further unpredictable whether the transfected cells will express a therapeutic level of the heterologous gene. The Examiner further contends that the types of vectors and the route of administration are relevant for enabling the claimed invention because each type of virus has different tropism and each vector system have different efficiency in transducing different types of cells. As support, the Examiner cites Robbins *et al.* (1998, Pharmacol. Ther. 80:35-47; "Robbins") for the teaching that each type of vector system has its unique advantages and limitations. The Examiner also cites Verma *et al.* (1997, Nature 389:239-42; "Verma") as teaching that "attempts to deliver genes in viral vectors has been confronted by these host response." The Examiner cites Miller *et al.* (1995, FASEB J. 9:190-199; "Miller") for the teaching that "no single delivery system is likely to be universally appropriate" and "targeting at the level of the vector has not been particularly well developed." For the reasons detailed below, Applicants respectfully assert that the rejection 35 U.S.C. § 112, first paragraph, for lack of enablement cannot stand and should be withdrawn.

Applicants respectfully assert that the specification of the present application coupled with information known as of the effective filing date of the present application provides sufficient guidance to enable one of skill in the art to administer the nucleic acid compounds of the present invention by any route, without undue experimentation. The specification of the application provides examples of a variety of routes for administering the nucleic acid compounds recited in the claims (see, *e.g.*, the specification at page 35, lines 2-4) and provides methods for assessing the therapeutic efficacy of the nucleic acid compounds administered by various routes of administration (see, *e.g.*, the specification at page 33, line 17 to page 34, line 21). The literature provides numerous examples of IL-12 adenoviral vectors administered by routes other than intratumoral administration, such as, *e.g.*, intranasal and intravenous administration (see, *e.g.*, Siders and Worth).

Applicants note that the localized response in the lungs of nude mice with osteosarcoma (OS) lung metastases following intranasal delivery of IL-12 adenovirus vectors, as described in Worth, was predictable because the route of administration was chosen to achieve a localized response in the lungs (see Worth at 3713, col. 2, fourth full paragraph). Moreover, while adenoviral vectors do show a preference for liver tissue when administered intravenously, delivery of IL-4 by an adenoviral vector was shown to be therapeutic for arthritis in a mouse model (see Kim *et al.*, 2000, Arthritis Res. 2:293-302; Ref. **C04**). In addition to intranasal and intravenous administration, adenovirus can be administered by other routes such as, for example, intramuscularly (see Etgen *et al.*, 1999, J. Biol. Chem. 274:22139-22142; Ref. **C05**). Thus, adenoviral vectors can be administered by a variety of routes.

Further, the literature provides guidance as to which viral or non-viral vector best suits a particular purpose. For example, Robbins teaches that "because each type of vector system has its unique advantages and limitations, each has applications for which it is best suited." See Robbins, abstract. Robbins teaches that retroviral vectors may be particularly suited to infect certain rapidly dividing cells, such as hepatocytes, tumor cells, and synovial cells lining inflamed joints. See Robbins at pg. 37, col. 1, second full paragraph. Robbins teaches that adeno-associated virus vectors may be suited for muscle and neuronal tissue. See Robbins at page 40, col. 2. Robbins teaches that adenoviruses can infect a wide variety of cells and that the host range can be altered by (1) modifying the fiber protein, (2) adding small binding epitopes specific for certain receptors, (3) coupling antibodies against tissue-specific cell surface proteins to the fiber

protein, and (4) using cell-specific promoters. See Robbins at pg. 37, col. 2, paragraph spanning pages 37-38.

Verma teaches that injection of lentivirus vectors by intravenous route in rodent brain, liver, muscle, eye or pancreatic-islet cells results in sustained expression and that it did not result in a cellular immune response to the vector. See Verma at pg. 240, col. 2, last paragraph and spanning page 241. Verma also teaches that adenoviral vectors can be modified to circumvent the immune response resulting in longer expression or particularly used to treat cancer, where the immune response will result in enhanced tumor killing. See Verma, pg. 241, cols. 1 and 2. Verma further teaches that adeno-associated vectors have been used to infect liver and muscle cells in immunocompetent mice. See Verma, pg. 241, col. 3.

Miller teaches that vectors can be targeted by the use of tissue-specific regulatory elements to restrict expression, *e.g.*, to skeletal and cardiac muscle or to B lymphoid cells. See Miller, pg. 195 col. 2, 1st full paragraph. Miller also teaches that retroviral vectors can be targeted, *e.g.*, to tumors in the central nervous system or to the liver. See Miller, pg. 196, paragraph spanning cols. 1 and 2.

Thus, Applicants respectfully assert that one of skill in the art would be able to choose an appropriate vector depending on the particular application, without undue experimentation. The fact that some embodiments may not work is irrelevant.

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.

Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984).

Accordingly, Applicants respectfully assert that the specification of the present application coupled with information known as of the effective filing date of the present application provides sufficient guidance to enable one of skill in the art to administer the nucleic acid compounds of the present invention by any route, without undue experimentation.

In view of the foregoing, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement cannot stand and should be withdrawn.

II. THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66 and 70 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Caruso *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:11302-11306 ("Caruso") taken with Melero *et al.*, 1997, Nat. Med. 3:682-5 ("Melero") and Kim *et al.*, 1998, *Eur. J. Immunol.* 28:881-890 ("Kim"). The Examiner contends that the ordinary skilled artisan would have been motivated to combine the methods taught by Caruso and Melero by administering a 4-1BB ligand of Melero in addition to the AdvIL-12 of Caruso for maximizing the tumor killing effect. The Examiner further contends that since Caruso and Melero each teach an agent that is effective in cancer therapy that shares a common mechanism of action, *i.e.*, an enhanced Th1 cell response and enhanced IFN-γ production, there is a reasonable expectation of success for an enhanced benefit of cancer killing. The Examiner concluded it would have been *prima facie* obvious to combine these agents to generate a new composition for the treatment of cancer with a reasonable expectation of success.

In response to Applicants' rebuttal evidence, the Examiner cited *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 for the proposition that "a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." As the Examiner notes, the evidence demonstrating greater than additive results for the sweeteners was insufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects.

The Examiner contends that the prior art consistently teaches that both IL-12 and 4-1BB would enhance the T-cell response/IFN production significantly when used in a combined therapeutic regimen. As support the Examiner contends that Hirschowitz demonstrates that the addition of IL-12 to a gp75 melanoma antigen vaccine resulted in a reduction in the number of metastases and that Kim demonstrates that 4-1BBL increased CD28-mediated IFN-γ production. Applicants respectfully disagree.

First, Applicants respectfully submit that there is no motivation to combine Caruso, Melero and Kim to administer IL-12 and 4-1BBL. The Examiner takes the position that one of skill in the art would expect that IL-12 and 4-1BBL act synergistically because of a common shared mechanism, *i.e.*, enhancement of Th1 response and increased IFN-γ production. However,

the prior art did not teach that these mechanisms were responsible for the roles of IL-12 and 4-1BBL in treating cancer. The mechanism for IL-12 anti-tumor activity was not understood. See, *e.g.*, Worth at pg. 3717 and Siders at pg. 54722. The literature merely speculates as to how IL-12 is functioning in treating cancer. Melero does not show anti-tumor effect of 4-1BBL without artificially enhancing 4-1BB on tumor cells. Kim merely discusses CD28 and 4-1BB co-stimulation in promoting Th1 cell responses, but does not demonstrate an anti-tumor effect at all. Moreover, the 4-1BB/4-1BBL system has been associated with production of a number of cytokines other than those associated with a Th1 response. For example, 4-1BBL has been associated with the production of IL-6, IL-8 and TNF-α and has a role in regulating the survival of B cells. See Cheuk *et al.*, 2004, Cancer Gene Therapy 11:215-226 at pg. 218, col. 2 (Ref. **C06)**. Because the mechanism of IL-12 anti-tumor activity was unclear and 4-1BBL was known to have an effect on cytokines other than those associated with a Th1 response, one of skill in the art would not have been motivated to combine Caruso, Melero, and Kim to administer the combination of IL-12 and 4-1BBL. Even assuming *arguendo* that there was a motivation to combine these references, based on the above, there was no reasonable expectation of success. At most, there is merely a suggestion to try.

Second, Applicants respectfully submit that the Examiner has not demonstrated that the prior art teaches that IL-12 and 4-1BBL would enhance the T-cell response and IFN-γ production in a synergistic manner. The combination of Hirschowitz and Kim does not teach that IL-12 and 4-1BB would enhance the T-cell response and IFN-γ production. Hirschowitz does not even mention 4-1BBL. Moreover, with respect to the combination of IL-12 and gp75, Hirschowitz is silent on the effect on an enhanced T cell response and IFN-γ production. Instead, Hirschowitz suggests that the synergism seen with IL-12 and gp75 for anti-tumor activity is based on activation of NK cells. See Hirschowitz, pg. 836, col. 1. This enhanced NK activity is believed to complement the T-cell immunity induced by the gp75 antigen. See id. at pg. 939, col. 1. Thus, Hirschowitz does not teach or suggest that both IL-12 and gp75 would enhance the T-cell response and IFN production, much less that IL-12 and 4-1BB would enhance the T-cell response and IFN production.

Kim does not remedy the deficiencies of Hirschowitz. Kim teaches that the combination of anti-CD28 and anti-4-1BB resulted in increased IFN-γ production. Kim teaches that synergistic effects can be seen with two co-stimulatory molecules. See Kim, pg. 881, col. 2. Kim teaches that this synergism may be due to activation of T cells at different stages. See Kim, pg.

886, paragraph spanning cols. 1 and 2. However, Kim does not provide any results with IL-12 nor provide any indication that IL-12 would be involved in a T cell response and IFN-γ production. Thus, Kim does not teach that IL-12, a cytokine, and 4-1BB, a co-stimulatory molecule, would enhance the T-cell response and IFN production. Furthermore, Kim does not show a decrease in metastasis or tumor growth. A decrease in metastasis or tumor growth was not even tested.

Accordingly, the combination of Hirschowitz and Kim does not teach a reduction in metastasis or tumor growth. Further, no common mechanism is taught, so one of skill in the art cannot arrive at a synergistic effect. Thus, contrary to the Examiner's contention, the prior art does not consistently teach that both IL-12 and 4-1BB would enhance the T-cell response/IFN production significantly when used in a combined therapeutic regimen. Accordingly, there is not a general expectation of obtaining greater than additive effects with a combination of IL-12 and 4-1BB ligand.

In summary, the present case can be distinguished from *Ex parte NutraSweet*. In *Ex parte Nutrasweet*, the prior art provided a general expectation of obtaining greater than additive effects with a combination of sweeteners. Prior art providing evidence that greater than additive results would be expected with 4-1BB and IL-12 has not been provided in this case. Thus, the prior art has not demonstrated a general expectation of obtaining greater than additive effect with a combination of IL-12 and 4-1BBL. Accordingly, Applicants respectfully re-submit that unexpected results are provided within the specification and are sufficient to overcome the *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully assert that the rejections under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Applicants respectfully request that the foregoing amendments and remarks be entered and made of record in the present application. Withdrawal of all of the rejections and consideration of the amendments are requested. An allowance of the application is earnestly sought. If any issues remain, the Examiner is respectfully invited to telephone the undersigned.

Respectfully submitted,

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